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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/987,763 | 11/15/2001 | Corey M. Crafton | 1533.1940002/MAC/MBT | 7167 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/987,763 | CRAFTON ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-21 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-21 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## *DETAILED ACTION*

*Clams 3 and 23-24 and 39-73 are canceled.*

*Claims 1-2, 4-21 and 25-38 are pending and are examined in this office action.*

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/23/05 has been entered.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***703-872-9306****.*

*The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.*

### *Claim Rejections - 35 USC § 101*

Claims *1-2, 4-21 and 25-38* stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility for the same reasons of record as set forth in the office action mailed on 06/28/05

The instant claims are drawn to an isolated DNA sequence (SEQ ID NO:7) or any variant thereof that is capable of regulating the transcription of a gene or interest. The specification asserts that the nucleic acid sequence of SEQ ID NO:7 is a putative gene identified by sequence homology that is responsive to putative regulatory molecule like pyruvate (Spec. page 23 table-1A). However the specification as filed fails to disclose that nucleic acid sequences of SEQ ID NO:7 is a regulatory sequence that regulates transcription of a gene of interest in general or in response to pyruvate.

The instant invention is not considered to have a specific and/or substantial utility, since the instant specification fails to establish that that the disclosed polynucleotide sequence (SE ID NO:7) is a transcription regulatory element explicitly or implicitly as putatively considered by the instant specification. The asserted transcription activity is mere computer-generated hypotheses, since no biological function has been established. The specification fails to disclose a functional assay that would enable one skill in the art how to evaluate the biological activity of the regulatory element encoded by SEQ ID NO:7. In addition the specification fails to establish any nexus between pyruvate metabolism and a regulatory element encoded by SEQ ID NO:7. Considering the applicant's disclosure, it is unclear whether pyruvate would up-regulate or down-regulate the transcription a gene operatively linked to the nucleic acid sequences of SEQ ID NO:7. The official sequence search using the disclosed nucleic acid sequences fails to provide any evidence that the polynucleotides of SEQ ID NO:7 is transcriptional regulatory element that is responsive to pyruvate.

In addition, the scope of invention as claimed encompasses any and all variants of nucleotide sequence of SEQ ID NO:7 that encodes any or a pyruvate responsive transcriptional element. The variations as claimed encompasses conserved motifs that are considered germane to the pyruvate responsive transcriptional activity. It is general knowledge in the art that even conservative nucleotide substitutions can adversely affect the transcriptional site and corresponding biological activity if nucleic acids sequences that are critical for such functions are substituted, added or deleted. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). The specification even fails to define what comprises the minimal structure or consensus core structure that defines the functional domain of the regulatory element present in the nucleic acid sequences of SEQ ID NO:7. In view of the foregoing, one skilled in the art would not readily attribute that the nucleic acid sequence or any variant thereof as claimed is a pyruvate responsive transcriptional element. Therefore, the asserted use for the claimed invention is not supported by either a specific and/or

substantial utility, since no function can be ascribed to the nucleic acid sequence as claimed. The only immediate apparent utility for the instant invention would be further scientific characterization of the claimed nucleic acid sequences a putative pyruvate responsive transcriptional element.

**Response to arguments**

The applicant argues that the earlier Office Action does not establish a prima facie case of lack of utility, because it does not consider all of the asserted utilities in the application. The applicant argues that even if the Office Action did establish a prima facie case of lack of utility, such a prima facie case would be overcome by the specifc and substantial utilities presented in the application. The applicant argues that the accepted commercial utility of increased transcription of a promoted polynucleotide is well-established and substantial. The applicant argues that the Office has dismissed the valuable insight provided by the b-galactosidase activity as disclosed in the application. The applicant concluded that the b-galactosidase activity is indicative of the regulator activity and such an activity alone would be sufficient to demonstrate utility of the claimed invention.

TABLE 1A

Nucleotide sequences that can be used to regulate gene expression

| Seq. I.D. NO: | Gene* | Regulatory Molecule† |
|---|---|---|
| 1 | pta | acetate |
| 2 | aceA | acetate |
| 3 | aceB | acetate |
| 4 | adh | ethanol |
| 5 | aldB | ethanol |
| 6 | poxB | pyruvate |
| 7 | ldh | pyruvate |
| 8 | amyB | carbon |
| 9 | malZ | carbon |
| 10 | bglX | carbon |
| 11 | gam | carbon |
| 12 | glgX | carbon |
| 13 | hisD | histidine |
| 14 | pyrR | pyrimidine |
| 15 | purD | purine |
| 16 | hrcA | temperature |
| 17 | htpX | temperature |
| 18 | dnaK | temperature |
| 19 | etc | temperature |
| 20 | grpE | temperature |
| 21 | clpB | temperature |
| 22 | narA | oxygen |

Sequence I.D. NOs 1, 2, and 3 have been previously described. The remaining sequences were discovered in ADM's *Corynebacterium glutamicum* genome sequencing project.
*Putative genes regulated by sequence I.D. NOs 4–22 were determined by homology to genes identified in other organisms, e.g., *Escherichia coli* or *Bacillus subtilis*.
†Putative regulatory molecules associated with the regulatory regions of SEQ I.D. NOs 4–22 were determined by analogy to regulatory regions identified in other organisms.

However, applicant's argumetns are found NOT persuasive. The specification asserts that the nucleotide sequences of SEQ ID NO:7 is a ***putative ldh-like*** *gene* that is regulated by pyruvate. *See Specification table 1A.* The specification fails to provide any

evidence which establishes that the SEQ ID NO:7 encodes a *ldh-like* responsive element that is regulated by pyruvate.

Furhtermore regarding applicants assertion that regulation of transcription of a reporter gene like β-galactosidase in cell is a specific asserted utility, this is found not persuasive because non-specific regulation of a reporter gene like β-gal is not a specific asserted-utility and is not considered as a well-established utility. As stated earlier the instant invention is not considered to have a specific and/or substantial utility, since the specification as filed fails to establish that that the disclosed polynucleotide sequence (SE ID NO:7) is a transcription regulatory element explicitly or implicitly as putatively considered by the instant specification.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Therefore, the asserted use for the claimed invention is not supported by either a specific and/or substantial utility, since no function can be ascribed to the nucleic acid sequence as claimed (*see Revised Interim Utility Guidelines*). The only immediate apparent utility for the instant invention would be further scientific characterization of the claimed nucleic acid sequences a putative pyruvate responsive transcriptional element. Therefore, the asserted use for the claimed invention is not supported by either a specific and/or substantial utility, since no function can be ascribed to the nucleic acid sequence as claimed. The only immediate apparent utility for the instant invention would be further scientific characterization of the claimed nucleic acid sequences a putative pyruvate responsive transcriptional element.

***Claim Rejections - 35 USC § 112***

Claims *1-2, 4-21 and 25-38* stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, or the same reasons of record as set forth in the office action mailed on 06/28/05.

**Nature Of Invention:**

Invention relates to a DNA sequence that regulates transcription of a gene operatively linked to the DNA sequence

**Breadth Of Claims And Guidance Provided By The Inventor:**

The instant claims are drawn to an isolated DNA sequence (SEQ ID NO:7) or any variant thereof that is capable of regulating the transcription of a gene or interest. In addition the claims are further drawn to expression vector and host cells comprising the claimed nucleic acid sequence or any variant thereof. The specification asserts that the nucleic acid sequence of SEQ ID NO:7 is a putative gene identified by sequence homology that is responsive to putative regulatory molecule like pyruvate (Spec. page 23 table-1A). However the specification as filed fails to disclose that nucleic acid sequences of SEQ ID NO:7 is a regulatory sequence that regulates transcription of a gene of interest in general or in response to pyruvate.

The instant specification fails to establish that that the disclosed polynucleotide sequences (SE ID NO:7) is a transcription regulatory element explicitly or implicitly as putatively considered by the instant specification. The asserted transcription activity is mere hypotheses base upon sequence comparison, since no biological function has been established. The specification fails to disclose any functional assay that would enable one skill in the art how to evaluate the biological activity of the regulatory element encoded by SEQ ID NO:7. In addition the specification fails to establish any nexus between pyruvate metabolism and the regulatory element encoded by SEQ ID NO:7. Considering the applicant's disclosure it is unclear whether pyruvate would up-regulate or down-regulate the transcription a gene operatively linked to the nucleic acid

sequences of SEQ ID NO:7. The official sequence search using the disclosed nucleic acid sequences fails to provide any evidence that the polynucleotides of SEQ ID NO:7 is transcriptional regulatory element that is responsive to pyruvate.

In addition, the scope of invention as claimed encompasses any and all variants of nucleotide sequences that encode a pyruvate responsive transcriptional element. The variations as claimed encompasses the conserved motifs that are germane to the pyruvate responsive transcriptional activity. It is general knowledge in the art that even conservative nucleotide substitutions can adversely affect the transcriptional site and corresponding biological activity if nucleic acids sequences that are critical for such functions are substituted, added or deleted *(supra).* Furthermore making and testing a point mutation is significantly different from the making and testing nucleic acid sequences wherein unknown number of nucleotides are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. In the instant case the specification even fails to disclose a functional assay that would enable one skill in the art how to evaluate the biological activity of the regulatory element encoded by SEQ ID NO:7. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the proposed transcriptional and/or functional activity. In addition determining biological activity of a transcriptional elements base upon sequence similarity alone is not considered routine in the art and without sufficient guidance to a specific transcriptional motif and a functional assay experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to practice the invention as claimed. The quantity of experimentation

required would include the functional characterization of polynucleotides of SEQ ID NO: 7 as a transcriptional regulatory element that is responsive pyruvate.

**Response to argument**

The applicant argues that, since the invention as claimed has specific and well-asserted utility the invention as claimed is fully enabled. However, applicant's arguments are found not persuasive for the reasons of record and as stated above that invention as claimed lacks a specific asserted utility or a well-established utility. Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to practice the invention as claimed. For example, the specification as filed fails to disclose that an isolated polynucleotide comprising any fragment of nucleotide of SEQ ID NO;7 as claimed is capable of regulating the transcription of a reporter gene in response to pyruvate. Therefore the undue experimentation required would include the functional characterization of polynucleotides of SEQ ID NO: 7 as a transcriptional regulatory element that is responsive pyruvate.

***Conclusion***

No claims are allowed.

This is a RCE of applicant's earlier Application No. 09/987763. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

**SUMESH KAUSHAL**
**PRIMARY EXAMINER**
**ART UNIT 1633**